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Factors Associated with Liver Biopsy Performance in HCV–HIV Coinfected Injecting Drug Users With HCV Viremia: Results From a Five-Year Longitudinal Assessment

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ABSTRACT *The last international consensus conference about hepatitis C virus (HCV) treatment emphasized the importance of treatment for persons coinfected with HCV and human immunodeficiency virus (HIV). As liver biopsy precedes treatment, we aimed to identify factors associated with the performance of liver biopsy among HIV–HCV coinfected drug users during a 5-year follow-up to study their access to HCV treatment. Of the 296 patients followed in the HIV hospital departments of Nice and Marseilles and with retrievable records about HCV diagnosis and care, 166 were eligible for analysis having had detectable HCV RNA at least once during the study period. Overall, 45.2% of patients underwent liver biopsy during follow-up. Using proportional hazard models, predictors of having had a liver biopsy were high social support, complete abstinence from drug injection, and lack of immunosuppression as well as male gender, no history of multiple incarcerations, more recent onset of drug use, and an increase of liver enzyme levels. These results suggest that specific efforts should be devoted to HIV–HCV coinfected drug users to assist with stabilizing these patients to optimize their access to HCV care whenever possible.*

KEYWORDS *Cohort study, Drug use, HCV, HIV, Liver biopsy.*

INTRODUCTION

Since the introduction of highly active antiretroviral treatment (HAART), the increase of survival of patients living with human immunodeficiency virus (HIV) has exposed the negative role of hepatitis C virus (HCV) coinfection on patients'

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survival.[1–3] Unfortunately, HCV viral clearance may occur spontaneously in a small proportion of those who become infected.[4] More often, hepatic fibrosis progression occurs; this is accelerated in people who are also HIV infected.[5]

Consensus conferences in the United States and Europe on the treatment of chronic hepatitis C infection have promoted treatment in HIV-positive patients with good clinical profiles without evident immunodeficiency.[6,7] In the most recent (2002) French consensus conference,[8] HCV treatment was recommended in coinfected patients with CD4 cell counts greater than 0.2×10^9 cells/L and with detectable HCV RNA according to activity and fibrosis stage of liver disease evaluated by liver biopsy. Physicians were also advised to consider the motivation of the patient, patient adherence to treatments, and patient social support.

Depression must be treated and alcohol consumption must be reduced before initiation of HCV treatment. While active injection drug use is considered a contraindication to HCV treatment, some drug use in a patient on drug abuse maintenance treatment (DAMT) is not a limitation to HCV treatment. Before 2002, a liver biopsy was mandatory to assess the indication of antiviral therapy for HCV infection.[7] Since then, liver biopsy is longer mandatory, but it remains strongly recommended, especially among HIV coinfected patients.[8] Liver biopsy should only be considered for motivated and adherent patients whose clinical picture, virological status, and social profile are compatible with HCV treatment. Moreover, physicians must recommend liver biopsy only if HCV treatment can be offered to the patient a few weeks later. Liver biopsy therefore can be considered as a good proxy of access to HCV treatment.

A previous study carried out in the MANIF 2000 cohort at the beginning of the wide diffusion of HAART showed that sociobehavioral characteristics may influence access to HIV antiretroviral therapy,[9] especially among HIV-infected drug users, who are particularly vulnerable to social instability.[10] Using longitudinal data from the same cohort, we aimed to identify factors associated with the performance of liver biopsy in HIV–HCV coinfected injecting drug users (IDUs).

METHODS

The methods and baseline characteristics of this cohort have been described in detail elsewhere.[9,11]. From October 1995 through June 1998, MANIF 2000 enrolled a cohort of 467 participants infected with HIV through injecting drug use. At enrollment, all patients were screened for HCV infection with commercial enzyme immunoassays. Among them, 447 (95.7%) had detectable HCV antibody. Patients were scheduled for semiannual examination by HIV specialists.

Medical Data

HIV care providers completed a standardized medical form that gathered clinical, treatment, and laboratory data. Opinions of physicians about patient adherence to antiretroviral treatment and to scheduled visits and about patient drug dependence were also collected. HIV-related clinical and biological data such as CD4+ cell count, HIV RNA, clinical stage, and antiretroviral therapy (highly active or not) were prospectively abstracted from medical records.

Serum liver enzymes levels (alanine aminotransferase and aspartate aminotransferase) were recorded at each follow-up visit of the cohort. Abnormal liver enzymes levels were defined at each visit as at least one of the two enzymes levels above 2.5 times the threshold normal values of each laboratory at which the assay was

performed. When information about detection of HCV RNA, HCV genotype, stage of liver biopsy (when performed) using Knodell and/or METAVIR systems, [12,13] and HCV treatment was not available, it was retrieved from records for the year 2001.

Patient Sociobehavioral Characteristics

Every 6 months, trained nurses administered a questionnaire that gathered patient sociodemographic information and history of incarceration. Patients also completed a standardized self-administered questionnaire, including information about their drug abuse and related behavior, drug maintenance treatment (buprenorphine or methadone), and alcohol consumption (measured in alcohol units [AU], with 1 AU corresponding to a glass of wine, a can of beer, or a measure of spirits and equivalent to 10–12 g alcohol)[14]. In the self-administered questionnaire, depression was measured by the CES-D scale,[15] and social support (from partner, family, and friends) was measured on a 5-point Likert scale.

Study Group

Among the 420 patients enrolled in the MANIF 2000 cohort in an HIV outpatient department in Nice or Marseilles, only those who had (1) at least one visit a year and 3 years of follow-up and (2) detectable HCV RNA at least one time during follow-up were considered eligible for data analysis. Such inclusion criteria were adopted to choose patients who could be recommended a liver biopsy. The first criterion was chosen considering that the lack of a regular follow-up is not compatible with a prescription for an antiviral treatment for HCV, which requires regular surveillance of the patient's HCV clinical status. Moreover, patients who underwent a liver biopsy before the 6 months prior to enrollment were excluded from data analysis.

Statistical Analysis

For each patient, only the first liver biopsy during the study period (between the 6 months before enrollment and the 66th month follow-up visit) was considered. Kaplan-Meier curves were calculated and compared throughout the different strata defined by each categorical variable using a log-rank test to evaluate the impact of each possible predictor on liver biopsy performance. Cox models were used to calculate crude and adjusted relative hazards, here referred to as relative risks (RRs). A variable was considered a candidate for entering the final model if its P value was less than .20 in the univariate analysis (log-rank test or univariate Cox regression model). For all factors considered eligible for the final model, the proportional assumption was always verified. Age and gender were introduced as putative confounders in the final model. All analyses were performed using SPSS software (v. 11.0).

RESULTS

Descriptive Analysis

Among the 420 patients enrolled in Marseilles and Nice in the MANIF 2000 cohort, 296 fulfilled the first initial selection criterion. Among these 296 patients, 88 (29.7%) never had HCV RNA measured, 27 (9.1%) were negative, and 181 (61.1%) were positive. Of these 181 patients who fulfilled the two selection criteria, 15 were excluded from analysis because they underwent a liver

TABLE 1. Distribution of sociodemographic and clinical characteristics at baseline in HIV–HCV coinfected individuals according to whether they underwent liver biopsy during follow-up (N = 166)

	Liver Biopsy		
	No (N = 91), n (%)	Yes (N = 75), n (%)	*P*
Mean age* (SD)	34.3 (5.2)	34.1 (4.5)	
Male gender	59 (64.8)	53 (70.7)	
Employment	33 (36.3)	40 (53.3)	†
High school certificate	13 (14.3)	11 (14.7)	
Living in a stable relationship*	41 (45.1)	36 (48.0)	
Stable housing*	54 (59.3)	49 (65.3)	
Multiple incarcerations‡	42 (46.2)	16 (21.3)	§
Median year of starting drug use (interquartile range)*	1982 (1978–1984)	1983 (1980–1985)	
Drug injection*	42 (46.2)	18 (24.0)	§
Alcohol consumption (>4 AU per day)*	19 (22.1)	17 (23.6)	
Genotype 3	21 (35.0)	14 (23.3)	
Aminotransferase levels >2.5*	9 (9.9)	12 (16.0)	
Median CD4+ cell count (interquartile range)*	380 (300–510)	400 (310–520)	
Mean HIV RNA (SD), log(cp)/ml*	4.0 (1.0)	3.9 (1.1)	
HIV clinical stage A*	62 (68.1)	52 (69.3)	
HAART treatment*	14 (15.4)	13 (17.3)	

*At enrollment, compared with the normal values of each laboratory where the assay was performed.
†$P < .05$.
‡In the 5 years prior to enrollment.
§$P < .01$.

biopsy before the study period. Finally, 166 patients were considered eligible for data analysis.

The genotype was available for 120 patients: 54.2% were infected with genotype 1, 2.5% with genotype 2, 29.2% with genotype 3, and 14.1% with genotype 4. Overall, 45.2% of eligible patients underwent their first liver biopsy during the study period. The incidence of first liver biopsy performance was 11.8 per 100 person-years over the study period.

Table 1 shows the distribution of clinical and sociodemographic characteristics at enrollment according to whether the patients underwent liver biopsy during the 5 years of follow-up. Among the 75 patients who underwent liver biopsy during follow-up, the METAVIR fibrosis severity score was distributed as follows: 13 (F0), 24 (F1), 20 (F2), 8 (F3), 6 (F4). Two patients had only a Knodell score (of 12 and 7) and for the 2 remaining patients, the fibrosis score could not be assessed. Of the 75 patients, 27 patients were treated for HCV during the follow-up with interferon alone or with interferon and ribavirin. Moreover, among the 91 patients who did not undergo liver biopsy, 4 (3 women and 1 man) received an antiviral treatment for the HCV infection. At enrollment, 21 (13%) individuals received methadone, and 19 (11%) were on buprenorphine maintenance treatment.

Univariate and Multivariate Analyses

Table 2 reports the associations between liver biopsy performance by sociobehavioral factors and clinical characteristics. In the univariate analysis, several clinical characteristics were predictive of liver biopsy performance: high liver enzyme levels

TABLE 2. Factors associated with the occurrence of liver biopsy during a 5-year follow-up of HIV–HCV infected individuals (N = 166)

	Univariate analysis			Multivariate analysis	
	Log rank *P* value	Crude RH	95% CI	Cox model Adjusted RH	95% CI
Male gender	.305	1.25	0.68–2.08	1.92	1.08–3.40
Employment*	.002	1.87	1.17–2.99		
Multiple incarcerations*	.004	0.45	0.25–0.79	0.44	0.24–0.82
Year of starting drug use†	.062	1.05	1.00–1.10	1.05	1.00–1.11
Drug injection‡	.011§	0.38	0.18–0.80		
Heroin use‡	0.175§	.68	0.39–1.19		
Complete abstinence from drug injection during follow-up	.002	2.12	1.29–3.57	2.07	1.21–3.56
Methadone maintenance treatment‡	.095§	0.53	0.26–1.11		
High support from partner*	.043	1.51	0.95–2.40		
High support from family*	.210	1.41	0.87–2.30		
Support from friends*	.010	1.74	1.09–2.79		
Support from partner, family, or friends*,‖	.095	1.36	1.08–1.72	1.30	1.01–1.68
Physician's perception about patient's low adherence to scheduled visits‡	.087§	0.50	0.23–1.11		
Physician's perception about patient's low adherence to antiviral therapy‡	.148§	0.56	0.26–1.23		
Aminotransferase level >2.5‡,¶	.003§	2.07	1.28–3.36	1.87	1.12–3.13
Number of visits with CD4+ cell count >500	.033	1.09	1.01–1.19	1.09	1.00–1.18
CD4+ cell count >500‡	0.052§	1.69	1.00–2.88		

CI, confidence interval; RH, relative hazard.

*At enrollment.

†These variables were used on a continuous scale.

‡Used as time-dependent variables in the model.

§For continuous or time-dependent variables, the *P* value was derived by the univariate Cox regression model.

‖It was calculated as a score. For example, patients who received high social support from the partner, family, and friends were given a 3.

¶Serum alanine aminotransferase (ALAT) levels or Serum aspartate aminotransferase (ASAT) levels greater than 2.5 times the corresponding threshold value.

and lack of immunosuppression, as expressed by either CD4 cell count greater than 0.5×10^9 cells/L at a given visit (as a time-dependent variable) or the number of follow-up visits at which patients had a CD4 cell count greater than 0.5×10^9 cells/L.

We also tested the effect of elevation of liver enzymes on the likelihood of undergoing a liver biopsy according to specific antiretroviral regimens (including ritonavir, nevirapine, or efavirenz, known to be associated with an increase incidence of transaminase elevation).[5] This analysis showed that, with respect to patients without transaminase elevation, undergoing liver biopsy was more common (RR=2.8) in individuals with transaminase elevation and on regimens including ritonavir, nevirapine. or efavirenz than individuals with transaminase elevation and on regimens not including such drugs. Liver biopsy was more frequently performed in patients who were employed; receiving high support from partner, family, or friends; and with no history of multiple incarceration. Concerning physician's opinion about patient's behavior, the physician's perceptions of a patient's low adherence to scheduled visits and to antiviral therapy seemed to negatively influence the decision of performing a liver biopsy.

Regarding drug use behaviors, liver biopsy was more frequently performed in individuals reporting complete abstinence from drug injection during follow-up, in those not reporting active drug injection or, more generally, heroin use at a given visit (both considered as time-dependent covariates), and in patients whose history of drug use was more brief. Patients who were on methadone maintenance treatment were less likely to have liver biopsy than the remaining patients. This association was not observed for patients on buprenorphine maintenance treatment. Alcohol consumption and cocaine use were not significantly associated with liver biopsy. It is interesting to note that physician's perception regarding patient's drug use was not associated with the outcome.

Finally, among patient sociobehavioral characteristics, having a biopsy was not associated with age, education level, living in a stable relationship, stable housing, depression, and time since HIV diagnosis. Furthermore, biopsy was not associated with the occurrence of AIDS-defining events during follow-up, receiving HAART, and having an undetectable HIV RNA.

After multiple adjustment using the Cox proportional hazard model (Table 2), men had a higher probability of undergoing liver biopsy than women (RR=1.92). However, when focusing on women, the number of children was not associated with liver biopsy at any visit (P=.42). Table 2 also shows that liver biopsy is more frequently performed in patients without immunosuppression and in those with elevated liver enzymes. In addition, liver biopsy was more common in patients who never reported injecting drug use during follow-up, and those with shorter drug use careers had higher chances of undergoing liver biopsy. However, biopsy was less common in those with a history of multiple incarceration and those with poor social support.

DISCUSSION

In this study, we focused on undergoing a liver biopsy as a proxy for access to antiviral treatment for HCV chronic infection. During a 5-year follow-up, nearly half of the patients with chronic HCV infection underwent a liver biopsy, a percentage that is higher than results from other surveys reported in HCV-infected drug users.[16] This proportion is also high considering that patients may be reluctant to undergo a liver biopsy because this procedure may often be associated with pain and sometimes with more severe complications, including death.[16,17] At

the time of the study, we found two groups of factors associated with biopsy performance: those directly related to recommendations of the last French consensus conference on HCV treatment[8] and those more related to the specificity of the cohort population.

In the first group of factors, biopsy was more often performed on patients with a stabilized HIV infection (high CD4+ cell count at several follow-ups), but less often in those with lower social support, which is consistent with recommendations to consider HCV treatment in HIV-infected people and the need for strong social support as an essential condition for positive outcomes.[8] Therapy is known to have distressing side effects, such as depression and fatigue,[5] that can interfere with a patient's daily life, and in such a context, psychological support supplied by family or friends may be crucial for long-term adherence to treatment.

Our results confirmed physicians' adherence to guidelines for individuals who reported active drug injection. Anyway, although DAMT has been shown to increase adherence to treatments among HIV-infected, opiate-dependant patients[11] and despite the enlargement of the French recommendations about HCV treatment to patients on DAMT, there was no difference in access to liver biopsy between patients on DAMT and those not on DAMT. Moreover, we found no association between elevated alcohol consumption and liver biopsy performance. At enrollment, only one fifth of the surveyed patients had elevated alcohol consumption, a proportion that is lower than that previously reported among HCV-infected drug users.[16] This low proportion of patients reporting elevated alcohol consumption may be explained by the fact that patients with chronic hepatitis C are usually educated to avoid alcohol, and there may also be a low tolerance for alcohol in HAART-treated patients who also have an HCV chronic infection.

Furthermore, we found an additional set of factors—history of prison, longer duration of drug use, and female gender—that was associated with not having a biopsy. Perhaps physicians may consider multiple incarcerations to be a proxy of irregular follow-up or continuous drug use, which can explain their reticence to recommend a biopsy. Duration of drug use may be used as a surrogate for duration of HCV infection.[4] It is worthwhile to note that this factor was associated with having a liver biopsy, even after controlling for other possible cofactors. Actually, liver biopsy was more frequently performed in patients who had started drug use more recently than in those with a longer career of injecting drug use (i.e., with possible longer duration of chronic HCV infection), although the latter are more likely to develop a severe HCV-related liver disease. This may be explained by the fact that patients recently infected with HCV have usually a better response to treatment than those infected earlier.[8]

Although female gender is usually associated with a better virologic response to antiviral therapy,[18,19] in our cohort, liver biopsy was performed less in women than in men. This result is consistent with other reports showing that women are less likely than men to undergo invasive procedures for the treatment of other diseases.[20] In addition, it has been reported in a French nationwide survey that liver biopsy–related pain was independently associated with female sex, hepatitis C, general anesthesia, and experience of the operator. Anxiety was also increased in women.[17] Consequently, women may be more reluctant to undergo liver biopsy than men. Pregnancy is a formal contraindication to HCV treatment, but we did not found any relation between the number of children and liver biopsy.

The association found between liver biopsy and methadone treatment in the univariate analysis may be because of the fact that, in France, methadone prescription

is recommended for IDUs with longer drug use careers, and buprenorphine is more often prescribed to IDUs with shorter drug use careers. Being on methadone treatment is a proxy for longer drug use career, an independent determinant of disease outcome.

Finally, in our survey, liver biopsy was more common in those with elevation of liver enzymes. Elevation of liver enzymes is often used as a treatment criterion in HCV-infected people without HIV infection, even if there is a poor correlation between levels of liver enzymes and histologic features of the liver.[17] In HIV-infected individuals, antiretroviral drug use has been associated with hepatotoxicity and major elevation of liver enzymes levels.[5,21] As liver biopsy was more common in those with elevated levels of transaminase and a regimen including ritonavir, nevirapine, or efavirenz than in those with elevated levels of transaminase on other regimens, this result may also be interpreted as a kind of dose–response relationship between the "severity" of elevation of liver enzyme and the physician's decision about performing a liver biopsy. However, as the elevation of liver enzymes does not constitute a criterion for recommending liver biopsy, the use of such a criterion indirectly increases the probability of undergoing liver biopsy in patients on specific antiretroviral regimens.

Unfortunately, it was impossible with our data to make the distinction between lack of biopsy recommendation and patient refusal. If some patients refused the biopsy, it is likely that their choice may have been influenced by the way that their HCV clinician offered the liver biopsy. Moreover, our assessment of drug use was based solely on patient self-report, but the validity and reliability of self-reports about active drug use have been established in many studies that used similar methods for collecting information about addiction behaviors,[22,23] as well as in a previous study in which we documented high agreement between self-reported heroin use and morphine detection in urine.[24] Because the French Social Security guarantees free-of-charge access to care, including medical evaluation and liver biopsy, to all individuals, our results may be generalized to all French HIV–HCV infected IDUs who accept medical follow-up. In contrast, they cannot be generalized to IDUs in countries where universal access to care is limited.

CONCLUSION

Our results showed physicians adhered to consensus recommendations about HCV care, although they tended to overweight the importance of elevated liver enzymes when referring HIV-infected patients for HCV treatment. Adherence to the recommendations in the strict sense may be de facto responsible for limited access to HCV care for active drug users or individuals without effective social support. Of course, the new index of biochemical markers[25] will probably reduce the necessity for liver biopsy and will improve access to HCV treatment for a subset of people reluctant to undergo invasive procedures. As recommended in the last consensus documents, therapeutic indications should be enlarged in drug users as they often have a good response to therapy.[8] More attention should also be devoted to women when offering a liver biopsy to HIV–HCV coinfected patients.

The prevalence of HCV infection among IDUs is high (from 75% to 90%),[26] and the majority of new cases still occur in this population, in which social instability is very common and is known to play a crucial role in lack of treatment adherence.[10] Expanding availability of drug maintenance treatments could also be a way to improve social and psychological stability in this population and then access to HCV treatment. In any event, more attention should also be devoted to these

patients to provide them a multidisciplinary approach, including HIV specialists, HCV specialists, psychologists, social workers, and community-based organizations, to optimize their access to HCV care whenever possible.

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